UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/551,874	05/07/2007	Stefan Russwurm	3535.027	3945

41288 7590 11/24/2009

PATENT CENTRAL LLC
Stephan A. Pendorf
1401 Hollywood Boulevard
Hollywood, FL 33020

EXAMINER	
KAPUSHOC, STEPHEN THOMAS	
ART UNIT	PAPER NUMBER
1634	
MAIL DATE	DELIVERY MODE
11/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/551,874	RUSSWURM ET AL.	
	Examiner	Art Unit	
	STEPHEN KAPUSHOC	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 August 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10,12-37,39-56,60 and 61* is/are pending in the application.

4a) Of the above claim(s) *1,3,8,12,14,20,21,30-37,39-56 and 60* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *2,4-7,9,10,13,15-19,22-29 and 61* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *05/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-10, 12-37, 39-56, 60 and 61 are pending.

Claims 1, 3, 8, 12, 14, 20, 21, 30-37, 39-56, and 60 are withdrawn from examination as detailed in the previous Office Action of 03/05/2009 and as indicated below.

Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are examined on the merits.

This Office Action is in reply to Applicants' correspondence of 08/31/2009 and 09/01/2009.

Applicants' remarks and amendments have been fully and carefully considered but are not found to be sufficient to put the application in condition for allowance. Any new grounds of rejection presented in this Office Action are necessitated by Applicants' amendments. Any rejections or objections not reiterated herein have been withdrawn in light of the amendments to the claims or as discussed in this Office Action.

This Action is made **FINAL.**

Please Note: The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

1. Applicant's remarks regarding traversal of the restriction requirement and the alleged unity of invention of different claimed methods (p.40-45 of the Remarks of 08/31/2009) have been fully and carefully considered but are not found to be persuasive. The Examiner maintains that the alleged common technical feature (use of body fluids for measurement of gene expression profiles) is not a special technical feature. For example, Anderson et al US PG Pub 2003/0194752 A1 (publication of application 10/400,275, with priority to the filing on 04/02/2002) provides for the quantitative analysis of marker biomolecules from body fluids.

It is noted that claims 12, 20, 21 and 60 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as the claims require only non-elected combinations of markers.

Priority

2. Acknowledgment is made of Applicant's indication that a request has been made of the International Bureau for the priority documents to be electronically transferred to the US Receiving Office.

Withdrawn Objection to the Claims and Specification - Sequence Compliance

3. The objection to the specification and claims for not complying with the sequence rules, as set forth on page 4 of the Office Action of 03/05/2009, is **WITHDRAWN** in light of the amendments to the specification and the claims.

Withdrawn Objection to the Specification

4. The objections to the specification, as set forth on pages 4 and 5 of the Office Action of 03/05/2009, are **WITHDRAWN** in light of the amendments to the specification .

Withdrawn Claim Objections

5. The objections to claims 2 and 13, as set forth on pages 5 and 6 of the Office Action of 03/05/2009, are **WITHDRAWN** in light of the amendments to the claims. Claim 2 is objected to over recitation of the phrase 'isolating of sample RNA from a sample of a mammal', where the phrase 'isolating sample RNA from a sample from a mammal' is correct.

New Claim Objections

6. Claim 61 is objected to for the specific recitation of non-elected subject matter. Applicants have elected for the specific combination of genes with the sequences as set forth in the first 57 sequences identified in the Table on pages 13-14 of the Remarks of 11/20/2008. Claim 61 encompasses any combination of 'SEQUENCE ID No, I.1 to SEQUNCE ID No. I.6242', thus encompassing numerous combinations and subcombinations of sequences different than the specific elected combination. It is noted that no claim is allowed in this Office Action. Upon allowance of a claim directed to the elected invention, the Examiner will consider rejoinder of the subject matter of the non-elected combinations, and rejoinder of any combinations that include all of the limitations of the allowed elected subcombination. Prior to allowance, any non-elected subject matter that is not re-joined with the elected subject matter will be required to be removed from the claims.

Appropriate correction is required.

Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

7. The rejections of claims 2 and 13 under 35 USC 112 2nd paragraph, as set forth on pages 6 and 7 of the Office Action of 03/05/2009, are **WITHDRAWN** in light of the amendments to the claims.

New Claim Rejections - 35 USC § 112 2nd ¶ - Indefiniteness

8. Claims 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 is unclear over recitation of the phrase 'the immobilized probes' because there is a lack of sufficient antecedent basis for any 'immobilized probes'.

Claim 27 is unclear over recitation of the phrase 'the cDNA probes' because there is a lack of sufficient antecedent basis for any 'cDNA probes'.

Claim 28 and 29 are unclear over recitation of the phrase 'the individual cDNA molecules' because there is a lack of sufficient antecedent basis for any 'individual molecules' probes'

See MPEP 2173.05(e).

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Written Description Newly Applied to Claims as Necessitated by Amendments

9. Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicants may wish to consult the Written Description Training Materials revised March 25, 2008, available online at www.uspto.gov/web/menu/written.pdf.

The rejection of claims for lack of adequate written description is relevant to the rejected claims, drawn to methods for in vitro diagnosis of sepsis and/or sepsis-like

condition, as they require RNA or DNA 'being a gene or gene fragment specific for sepsis' (as recited in independent claims 2 and 13), and encompassing 'gene fragments thereof with' as few as 5 nucleotides (as recited and encompassed by claims 13 and 61). In the instant case the specification does not provide the skilled artisan with written description that adequately identifies characteristics of particular nucleic acids suitable for performing the claimed method as generically encompassed by the claims (i.e. the claims generically require nucleic acids with the functionality of being 'specific for sepsis') as well as methods requiring minimally 5 nucleotides of the sequences recited in claims 13 and 61.

Relevant to the lack of particular structural limitations in the rejected claims, MPEP 2163 states:

> The claimed invention as a whole may not be adequately described if the claims require an essential or critical feature which is not adequately described in the specification and which is not conventional in the art or known to one of ordinary skill in the art.

In the instant case, genes as generically encompassed by the claims wherein the expression is diagnostically indicative of sepsis or sepsis-like conditions are not known in the prior art (as generically recited in the claims, encompassing any genes or gene fragments from the human genome). Further, while the specification asserts that there is a group of genes from humans that are differentially expressed in humans with sepsis as compared to a non-septic individual (i.e. Tables 8 and 9), there is no disclosed relationship between the structure of the genes (i.e. their nucleotide sequences) and their functionality (i.e. diagnostic of sepsis) such that the skilled artisan would recognize that Applicants are in possession of the methods as generically claimed which

encompass the use of any gene or fragment thereof. This is also relevant to the breadth of claims 13 and 61, which, consonant with the election, which encompasses any genes comprising as few as 5 nucleotides of the mRNA sequences as elected.

In conclusion, having considered the breadth of the claims, and the particular teachings of the instant specification, and the teachings of the prior art, the specification, while providing a written description of methods requiring the step of, for example:

> Comparing the abundance of particular mRNA species from a sample to the abundance of the same mRNA species from a control sample, wherein the mRNA species comprise SEQ ID NOs: 220, 3O3, 529, 754, 844, 1705, 2370, 2449, 2468, 2481, 2709, 2831, 2928, 2948, 3068, 3079, 3209, 3268, 3305, 3317, 3331, 3399, 3424, 3433, 3482, 3508, 3523, 3624, 3676, 3765, 3796, 3873, 3879, 3881, 3917, 4060, 4096, 4122, 4141, 4268, 4328, 4450, 4528, 4609, 4654, 4695, 4705, 4937, 5265, 5338, 5418, 5542, 5567, 5647, 5779, 6018 and 6200

does not provide an adequate written description of the broadly claimed subject matter.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of an adequate written description. Applicants' arguments (p.48-50 or Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Applicants have argued that the specification sets forth Tables 2, 3, 8 and 9 which provide the sequences of cDNAs significantly overexpressed and underexpressed, and indicative of SIRS. The examiner maintains that the disclosure of particular specific genes in a sample from a SIRS patient is not adequate to provide a description of the generically claimed methods that encompass the analysis of any gene

from the human genome. Additionally, the breadth of the claims as requiring minimally 5 nucleotide of the recited sequences of claims 13 and 61 can be demonstrated by an exemplary analysis of SEQ ID NO: 303, which is required by claims 13 and 61; the first 5 nucleotides of SEQ ID NO: 303 are TTTTT, and thus while the specification may assert a role of an mRNA comprising SEQ ID NO: 303 in sepsis or SIRS diagnosis, the claims are sufficiently broad to encompass the analysis of any gene minimally comprising TTTTT.

This issue, with regard to the written description requirement of 35 USC 112 1st ¶, is noted by Applicants on page 50 of the Remarks, where Applicants provide that there is no simple relationship between the structure of any gene and the function of the gene with regard to sepsis. Further, where Applicants argue that WO 03/002763 provides for specific genes that are known which are indicative of sepsis, the Examiner maintains that the cited while the cited prior art may provide listing of genes asserted to be associated with immune response and thus hypothesized to be indicative of sepsis, WO 03/002763 does not provide the skilled artisan with a teaching as to how one might use the listed genes to perform a quantitative analysis of gene expression to diagnose sepsis.

The rejection as set forth is **MAINTAINED**.

Maintained Claim Rejections - 35 USC § 112 1st ¶ - Enablement Newly Applied to Claims as Necessitated by Amendments

10. Claims 2, 4-7, 9, 10, 13, 15-19, 22-29 and 61 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s)

contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention and breadth of the claims

The claims are drawn to methods of diagnosis of sepsis and/or sepsis like conditions in human.

The claims generically encompass analysis of any gene or fragment specific for sepsis.

The claims encompass any comparison of any labeled RNA, as well as any fragments of the elected combination of SEQ ID NOs, or fragments minimally comprising 5 nucleotides of the recited SEQ ID NOs.

The claims encompass detection of any condition that can be considered a 'sepsis-like condition'.

The claims thus require knowledge of a correlative association between any expression levels of a wide variety of RNA combinations and a variety of different phenotypes in different subjects.

Direction provided by the specification and working example

Relevant to the Election, the instant specification provides a comparative analysis (Example 3 – p.26) of gene expression in two human individuals, one classified as a sepsis patient and the other classified as a non-septic control subject (Table 7). The specification provides asserts that 54 particular genes were overexpressed in the

sepsis-patient sample (Table 8), and 56 particular genes were under-expressed in the sepsis-patient sample (Table 9).

Relevant to the claims and the elected invention, the specification provides the aforementioned analysis of sepsis gene expression, but does not provide for gene expression in the generic 'sepsis-like conditions'.

The specification provides only the results of a comparison between two individual subjects (a single case and a single control), with no validation of the asserted particular mRNAs specific for sepsis, nor any analyses of populations of cases or controls. There is no statistical analysis of the reliability of classification using expression of particular mRNA species.

Additionally it is noted that the particular mRNAs asserted in the specification (Tables 8 and 9) to be indicative of sepsis are not included in the particular mRNAs of the Election.

State of the art, level of skill in the art, and level of unpredictability

While the state of the art and level of skill in the art with regard to determining the abundance of any particular nucleic acid biomarker or combination of biomarkers is high, the unpredictability associated with correlating any comparison of abundances with a particular phenotype such as sepsis, is even higher. Such unpredictability is demonstrated by the prior art, the post-filing art, and the instant specification.

Because the claims encompass comparing any abundances of any particular RNAs to any control RNAs, where the specification provides only the

example of analysis of two individuals (one case and one control), it is relevant to point out the unpredictability in using gene expression to establish a phenotype. For example, Cheung et al (2003) teaches that there is natural variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). Additionally, the prior art of Shalon et al (2001) teaches that preferably 20-50 different test individuals are assayed to obtain meaningful data showing a significant change in gene expression levels, and changes of gene expression of at least 2 fold and up to 100 fold or more are desirable for the comparison of gene expression levels between a case and control population (p.10 ¶156, ¶158). Further, it is known in the art that the p-value of any marker used to diagnose sepsis will change based on the size of the population used for comparison (PG Pub US 2004/0106142, p.14, ¶[0127]).

Given the lack of any statistical significance in the methods, it is relevant to point out that the prior art of Thisted (1998) provides guidance as to what is required to indicate that an association is statistically significant (Thisted teaches that it has become scientific convention to say that a P-value of 0.05 is considered significant (p.5

- What does it mean to be 'statistically significant'), and that values above the conventional reference point of 0.05 would not be considered strong enough for the basis of a conclusion).

Because claims encompass the analysis of gene expression in any body fluid, whereas the specification provides only expression in whole blood samples, it is relevant to point out the unpredictability in comparing gene expression among different tissues. Cobb et al (2002) teaches the unpredictability in analysis of gene expression different tissue sample types of a septic mammal, specifically in spleen and liver samples from septic mice. Notably, the reference teaches that, when compared to a non-septic sample, the relevant expression profiles of the septic mouse spleen and the septic mouse liver contain different nucleic acids at different levels (Table 1; p.2714, middle col., lns.2-8).

Quantity of experimentation required

A large and prohibitive amount of experimentation would be required to make and use the claimed invention. One would have to establish that any level of nucleic acid abundance of any RNAs (as generically encompassed by the claims), as compared to a control, is indicative of sepsis. Such experimentation would require case:control analysis of a population large enough to attain statistical significance, and require the analysis of different tissue types and analysis of any RNA species of interest. Even for the particularly elected SEQ ID NOs it is noted that the instant specification does not provide that these mRNAs are robustly and reliably diagnostic of the presence of sepsis or any other

condition that may be considered 'sepsis-like', nor does the specification provide that RNA minimally comprising 5 nucleotides of the recited RNAs, as encompassed by the claims, may be used in a method of sepsis diagnosis.

Conclusion

Taking into consideration the factors outlined above, including the nature of the invention and breadth of the claims, the state of the art, the level of skill in the art and its high level of unpredictability, the lack of guidance by the applicant and the particular examples, it is the conclusion that an undue amount of experimentation would be required to make and use the claimed invention.

Response to Remarks

Applicants have traversed the rejection of claims under 35 USC 112 1st ¶ for lack of enablement. Applicants' arguments (p.51-56 or Remarks) have been fully and carefully considered but are not found to be persuasive to withdraw the rejection.

Applicants have argued that the claims have been amended to recite genes for which a written description is provided. The argument is not persuasive as the Examiner maintains that the claims still encompass methods which are generic with regard to the RNA species required for analysis in the diagnosis of sepsis, and the claims still broadly encompass RNA species minimally comprising 5 nucleotides of the recited particular sequences.

Applicants have additionally argued that 'sepsis-like' conditions are typically recognized in a clinical setting by evaluation of subjective criteria. The Examiner maintains that the claims do not require, nor does the specification

provide, any limiting definition for 'sepsis-like' conditions. As such the claims are sufficiently broad to encompass anything reasonably considered to be 'sepsis-like', where phenotypes as diverse as fever, inflammation, and increased heart rate may be considered 'sepsis-like' as they may be components of sepsis.

Finally, Applicants have argued that "the specification provides highly statistically relevant correlation between gene expression and condition of sepsis" (p.55 of Remarks). However, the Examiner maintains that while the specification may show large differences in measures of gene expression, the specification in fact provides only the analysis of a single case and a single control subject. There is no validation of the asserted association, where given the teachings of the art cited by the Examiner to demonstrate the unpredictability of gene expression association studies, the Examiner maintains that it is unpredictable as to whether or not the associations asserted in the specification would hold true for any other individual subject or populations in general.

The rejection as set forth is **MAINTAINED.**

Withdrawn Claim Rejections - 35 USC § 102

11. The rejection of claims under 35 U.S.C. 102(b) as being anticipated by the prior art (as set forth on pages 14-15 of the Office Action of 03/05/2009, is **WITHDRAWN** in light of the amendments to the claims.

Conclusion

12. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen Kapushoc whose telephone number is 571-272-3312. The examiner can normally be reached on Monday through Friday, from 8am until 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached at 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days.

Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

/Stephen Kapushoc/
Primary Examiner, Art Unit 1634